Towards a multi-scale model of combination targeted and cytotoxic therapy to evaluate treatment response in HER2+ breast cancer

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Overview

- Using an established ODE model at the tissue scale for a preclinical model of HER2+ breast cancer undergoing trastuzumab treatment, expand to include cell scale effects for combination trastuzumab-paclitaxel therapy
- Will connect the two scales by coupling drug effects into the growth and reduction terms of the governing equation for tumor volume changes
- An integrated mathematical-experimental approach bridging *in vivo* and *in vitro* experimental data, and therefore multiple scales, may elucidate the potential best strategies for combination therapy for HER2+ breast cancer

Tissue Scale Model

- Five coupled, ODEs for the longitudinal relationship of vasculature, hypoxia, necrosis, immune infiltration, and tumor growth[3]

$$[1]\quad \frac{dT}{dt} = gT(1+\rho H) - \mu_T TI$$

$$[2]\quad \frac{dI}{dt} = \alpha_V V(1-I) + \alpha_N N(1-I) - \mu_I IT$$

$$[3]\quad \frac{dV}{dt} = \alpha_T T(1-V) + \alpha_I I(1-V) - \mu_V VT$$

$$[4]\quad \frac{dN}{dt} = \beta(1-V)(1-N) - \mu_N NI$$

$$[5]\quad \frac{dH}{dt} = \gamma(\delta - V)H(1-H)$$

Table 1: Definitions of model variables

Output	Description
T	Tumor volume
I	Fraction of immune response in tumor
V	Fraction of well-vascularized tumor
N	Fraction of necrosis in tumor
H	Fraction of hypoxia in tumor

Table 2: Definitions of model parameters

Parameter	Description
g	Tumor volume growth rate
ρ	Ability of hypoxia to promote tumor growth
μ_T	Rate tumor volume decreases due to immune response
α_N	Rate immune response increases due to necrosis
α_V	Rate immune response increases due to vasculature
μ_I	Rate immune response decreases per tumor volume
α_T	Rate vascularization increases per tumor volume
α_I	Rate vascularization increases due to immune response
μ_V	Rate well-vascularized tissue decreases per tumor volume
β	Rate necrosis increases due to decreased fraction of well-vascularized tumor
μ_N	Rate necrosis decreases due to immune response
γ	Rate hypoxia increases or decreases due to fraction of well-vascularized tumor
δ	Threshold for hypoxia to increase or decrease due to fraction of well-vascularized tumor

Figure 2: Diagram of the interactions in the model equations between the different biological components

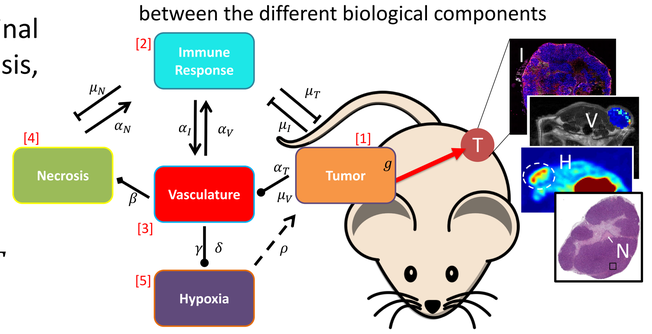
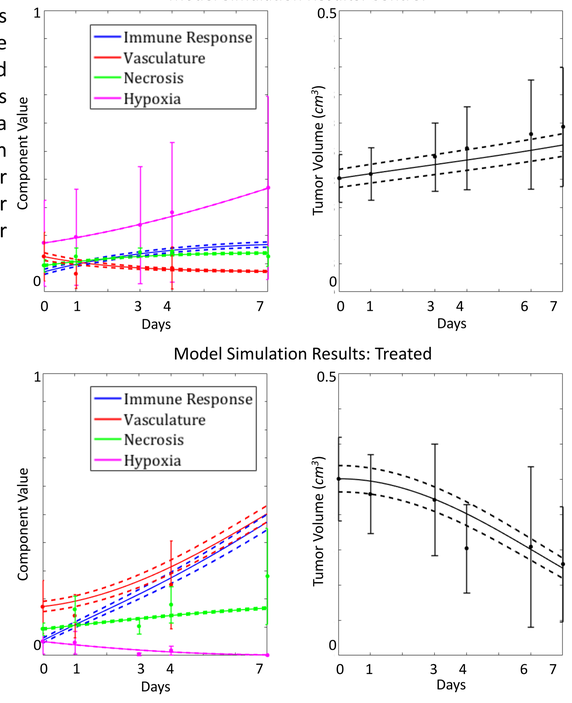


Figure 3: Model results with 95% confidence intervals indicated with dashed lines against validation data for tumor volume with 95% confidence error bars (right: tumor volume, left: tumor tissue components)



In vivo data

- Nude athymic mice subcutaneously implanted with BT474 HER2+ human breast cancer cells in the flank (allowed to grow for 4-6 weeks) and injected on days 0 and 3 with trastuzumab (10 mg/kg) or, in controls, with saline.
- Over 7 days, tumor volume, vasculature, necrosis, hypoxia, and immune response measurements quantified using several experimental methods (Table 1)
- Tumor volume collected using caliper measurements
- Physiological parameter for vascular perfusion and permeability, K^{trans}, derived from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) data for fraction of well-vascularized tumor
- Hematoxylin and eosin (H&E) staining for percent necrosis
- ^{18}F-fluoromisonidazole positron emission tomography (FMISO-PET) standard uptake values for percent hypoxia.
- Immunofluorescent imaging for CD11c & F4/80 myeloid markers for immune infiltration

Table 1: Summary of experimental data utilized and their sources

Data Type	Description
Tumor volume	Two separate sets recorded using caliper measurements[1,2]
Fraction of well-vascularized tumor	DCE-MRI data[1]
Fraction of necrosis in tumor	H&E stained histology data[1]
Fraction of hypoxia in tumor	FMISO-PET imaging data[2]
Fraction of immune response in tumor	Immunofluorescent stained histology data[3]

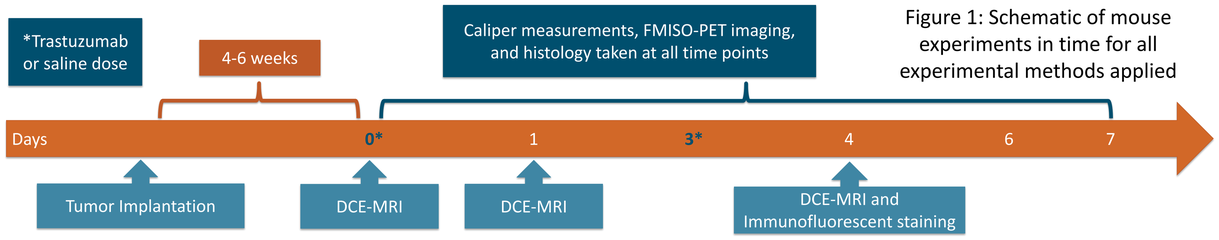
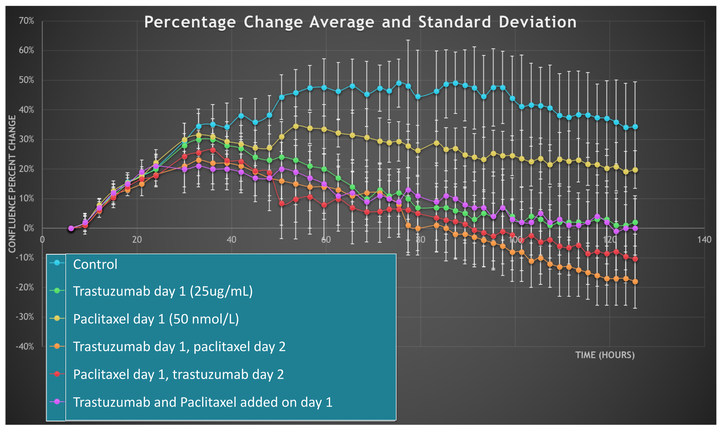


Figure 1: Schematic of mouse experiments in time for all experimental methods applied

In vitro data

- BT474 human derived breast cancer *in vitro* cell data measured by time-resolved microscopy
- Cultures treated with trastuzumab and/or paclitaxel on days 1 and 2 after cells are plated
- Change in confluence recorded over the course of seven days
- Trastuzumab dosing prior to paclitaxel potentially results in the greatest reduction in tumor cells

Figure 4: Preliminary *in vitro* results for cell culture data



Formulation for Combining *in vivo* and *in vitro* scales

$$\frac{dT}{dt} = g(1+\rho H)\left(1-\frac{T}{K}\right)T - dT - \mu_C TI$$

where $d = f_d(A_b, P_i, g)$
and $g = f_g(A_b)$

- Trastuzumab-HER2 binding decreases proliferation and causes signaling cascades that can lead to cell death
- Paclitaxel arrests proliferation during mitosis leading to cell death (and therefore its effectiveness depends on cellular proliferation rates)
- Drug efflux will depend on a threshold amount (γ) of the remaining previous drug dose

$$\frac{dA_f}{dt} = -\beta_A A_f T + \upsilon_A A_b$$

$$\frac{dA_b}{dt} = \beta_A A_f T - \upsilon_A A_b - \alpha_A A_b + \rho_A A_i$$

$$\frac{dA_i}{dt} = \alpha_A A_b - \chi_A A_i - \rho_A A_i$$

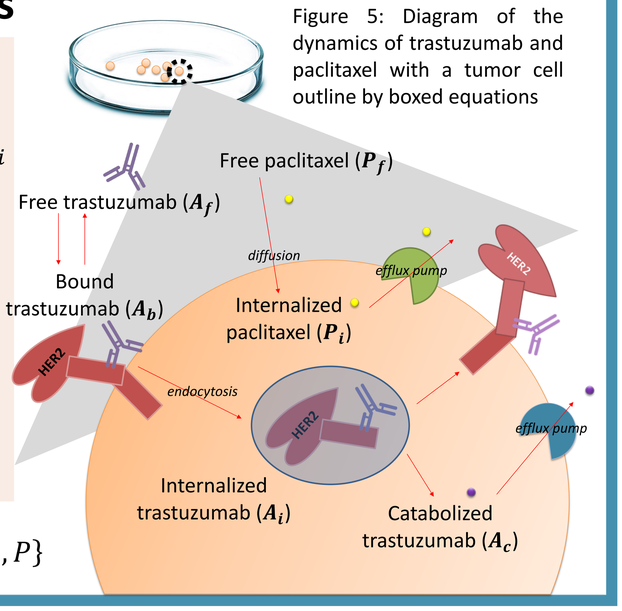
$$\frac{dA_c}{dt} = \chi_A A_i - f_\epsilon(\epsilon_A)A_c$$

$$\frac{dP_f}{dt} = -\alpha_P P_f T + f_\epsilon(\epsilon_P)P_i$$

$$\frac{dP_i}{dt} = \alpha_P P_f T - f_\epsilon(\epsilon_P)P_i$$

$$f_\epsilon(\epsilon_Y) = \begin{cases} \epsilon_Y, & Z < \gamma \\ 0, & Z \geq \gamma \end{cases} \text{ where } Y, Z \subset \{A, P\}$$

Figure 5: Diagram of the dynamics of trastuzumab and paclitaxel with a tumor cell outline by boxed equations



Next Steps

- Formulation of growth and death terms of the multiscale model
- Collect data for BT474 cells quantifying:
  1. Internalized paclitaxel
  2. Bound trastuzumab
  3. Internalized trastuzumab
  4. Catabolized trastuzumab
- Calibrate the multiscale model with *in vitro* data and make combination therapy predictions

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References:

1. Sorace, A.G., et al., Breast Cancer Res Treat, 2016. **155**(2): p. 273-284
2. Sorace, A.G., et al., Mol Imaging Biol, 2017. **19**(1): p. 130-137
3. Jarrett, A.M., et al., Under Review